



King's Research Portal

DOI:

[10.1038/npp.2017.221](https://doi.org/10.1038/npp.2017.221)

Document Version

Publisher's PDF, also known as Version of record

[Link to publication record in King's Research Portal](#)

Citation for published version (APA):

Cattaneo, A., & Pariante, C. M. (2017). Integrating 'Omics' Approaches to Prioritize New Pathogenetic Mechanisms for Mental Disorders. *Neuropsychopharmacology : official publication of the American College of Neuropsychopharmacology*, 43(1), 227-228. <https://doi.org/10.1038/npp.2017.221>

Citing this paper

Please note that where the full-text provided on King's Research Portal is the Author Accepted Manuscript or Post-Print version this may differ from the final Published version. If citing, it is advised that you check and use the publisher's definitive version for pagination, volume/issue, and date of publication details. And where the final published version is provided on the Research Portal, if citing you are again advised to check the publisher's website for any subsequent corrections.

General rights

Copyright and moral rights for the publications made accessible in the Research Portal are retained by the authors and/or other copyright owners and it is a condition of accessing publications that users recognize and abide by the legal requirements associated with these rights.

- Users may download and print one copy of any publication from the Research Portal for the purpose of private study or research.
- You may not further distribute the material or use it for any profit-making activity or commercial gain
- You may freely distribute the URL identifying the publication in the Research Portal

Take down policy

If you believe that this document breaches copyright please contact librarypure@kcl.ac.uk providing details, and we will remove access to the work immediately and investigate your claim.

and thus one can ‘fine-tune’ the pharmacological activity of the endogenous ligand. Such compounds could offer not only enhanced CB1R selectivity, but also reduced receptor down-regulation and inter-receptor promiscuity (Kulkarni *et al*, 2016). One such compound GAT211 increases CB1R effects, demonstrates good efficacy in rodent models of chronic pain without demonstrating acute tolerance, rewarding properties or dependence (Slivicki *et al*, 2017). Our preliminary data show that GAT211 also enhances fear extinction in auditory cue-induced fear conditioning model and could potentially provide a novel approach to PTSD drug development.

FUNDING AND DISCLOSURE

The work was supported by National Institutes of Health grants MH52619 to AS and DA027113 and EY024717 to G. A.T. GAT is a co-inventor on the patents filed by Northeastern University for the CB1 PAMS. The remaining author declares no conflict of interest.

Anantha Shekhar^{*1} and
Ganesh A Thakur²

¹Department of Psychiatry and Indiana Clinical and Translational Sciences Institute; Indiana University School of Medicine, Indianapolis, IN, USA;

²Department of Pharmaceutical Sciences, Northeastern University, Boston, MA, USA
E-mail: ashekhar@iu.edu

Gunduz-Cinar O, Hill MN, McEwen BS, Holmes A (2013). Amygdala FAAH and anandamide: mediating protection and recovery from stress. *Trends Pharmacol Sci* **34**: 637–644.

Kulkarni PM, Kulkarni AR, Korde A, Tichkule RB, Laprairie RB, Denovan-Wright EM *et al* (2016). Novel Electrophilic and Photoaffinity covalent probes for mapping the cannabinoid 1 receptor allosteric site(s). *J Med Chem* **59**: 44–60.

Neumeister A, Seidel J, Ragen BJ, Pietrzak RH (2015). Translational evidence for a role of endocannabinoids in the etiology and treatment of posttraumatic stress disorder. *Psychoneuroendocrinology* **51**: 577–584.

Pietrzak RH, Huang Y, Corsi-Travali S, Zheng MQ, Lin SF, Henry S *et al* (2014). Cannabinoid type 1 receptor availability in the amygdala mediates threat processing in trauma survivors. *Neuropsychopharmacology* **39**: 2519–2528.

Slivicki RA, Xu Z, Kulkarni PM, Pertwee RG, Mackie K, Thakur GA *et al* (2017). Positive allosteric modulation of cannabinoid receptor type 1 suppresses pathological pain without producing tolerance or dependence. *Biol Psychiatry* e-pub ahead of

print 06 July 2017; doi:10.1016/j.biopsych.2017.06.032.

Watts BV, Schnurr PP, Mayo L, Young-Xu Y, Weeks WB, Friedman MJ (2013). Meta-analysis of the efficacy of treatments for posttraumatic stress disorder. *J Clin Psychiatry* **74**: e541–e550.

Neuropsychopharmacology Reviews (2018) **43**, 226–227. doi:10.1038/npp.2017.230

OPEN

Integrating ‘Omics’ Approaches to Prioritize New Pathogenetic Mechanisms for Mental Disorders

Neuropsychopharmacology research is between a rock and a hard place. The rock is the historical, but slow, hypothesis-driven approach, where discovery occurs by testing candidate mechanisms in already well-known biological models. The hard place is the innovative, but overwhelming, hypothesis-free approach, where ‘omics’ analyses of everything that is analyzable generates a deluge of data implicating hitherto unknown mechanisms. So, either we have little data on things we already know, or too much data and cannot find the needle in a haystack. One solution is to mix apples and oranges: integrating cross-species and cross-tissues ‘omics’ data to find mechanisms that recur across different experimental and clinical models. The idea has been used with remarkable success. And yes, we will finish with the proverbs now.

Niculescu *et al* (2000) first developed and used such an approach, which they called convergent functional genomics. More recently, the approach has been used by them to help prioritize genes from genome-wide association studies (GWAS) of bipolar disorder (Patel *et al*, 2010), integrating GWAS findings, transcriptomics data on postmortem human brain and blood, and studies in animal models, to identify top-genes supported by all approaches. They identified six genes (*ARNTL*, *MBP*, *BDNF*, *NRG1*, *RORB*, and *DISC1*), which are involved in relevant

biological processes, such as circadian rhythm, connectivity, and neuroplasticity. They used a similar strategy for schizophrenia (Ayalew *et al*, 2012). Interestingly, this strategy could be done with publically available data rather than being based on novel experimental findings.

In 2013, we studied transcriptomics data from the hippocampus of adult prenatally stressed rats (an established animal model of depression with high glucocorticoid levels) and from a human neuronal stem cell line (that we treated with a concentration of cortisol that reduces neurogenesis) (Anacker *et al*, 2013). We found that TGFβ-SMAD2/3 and Hedgehog signaling are reduced in both models: TGFβ-SMAD2/3 promotes neurogenesis (and has been found to be reduced in depressed patients), whereas Hedgehog promotes neuronal differentiation (and has not been studied in depressed patients yet). Similarly, Malki *et al* (2016) studied transcriptomics from the prefrontal cortex of mice bred for high aggressive behavior and from the brain of zebrafish exposed to aggressive social encounters. They identified seven genes shared in both datasets, including HDAC4, which has genetic variants associated with aggressive behavior in mental retardation, and it is targeted by valproic acid, a pharmacological treatment for aggressive behavior. Finally, Luoni *et al* (2016) studied methylome analyses performed in multiple models of early life stress: rats exposed to prenatal stress (prefrontal cortex); human newborns exposed to stress in pregnancy (cells from the umbilical cord); and rhesus monkeys exposed to stressful rearing conditions (peripheral blood and prefrontal cortex). Their top gene was *Ank3*, a gene with a strong association for psychiatric disorders; and they also demonstrated an interaction between functional genetic variants within *Ank3* gene and obstetric complications on working memory in humans. Although these studies are predominantly ‘comparative’ in their nature, this cross-species and cross-tissues approach can be used to produce ‘integrative’ findings when it generates

novel lists of overlapping or functionally related genes through statistical or bioinformatic analysis.

With the collapse of R&D in mental health by pharmaceutical companies, convergent/integrative 'omics' approach represents a unique opportunity for the scientific community to mine existing datasets as well as data from experimental and clinical models, to prioritize targets for the psychotropic medications of the future.

FUNDING AND DISCLOSURE

AC and CMP are supported by the UK National Institute for Health Research (NIHR) Biomedical Research Centre at the South London and Maudsley NHS Foundation Trust and King's College London; and by the UK Medical Research Council, Grants MR/L014815/1 and MR/J002739/1. CMP has received research funding from pharmaceutical companies interested in the development of new antidepressants, such as Johnson & Johnson and Eleusis, but the work described in this paper is not related to this funding. AC does not have any conflict of interest.

Annamaria Cattaneo^{1,2} and Carmine M Pariante^{1,2}

¹Stress, Psychiatry and Immunology Laboratory, Department of Psychological Medicine, Institute of Psychiatry, Psychology & Neuroscience, King's College, London, UK; ²Biological Psychiatry Unit, IRCCS Fatebenefratelli S. Giovanni di Dio, Brescia, Italy
E-mail: carmine.pariante@kcl.ac.uk

Anacker C, Cattaneo A, Luoni A, Musaelyan K, Zunszain PA, Milanese E *et al* (2013). Glucocorticoid-related molecular signaling pathways regulating hippocampal neurogenesis. *Neuropsychopharmacology* **38**: 872–883.

Ayalew M, Le-Niculescu H, Levey DF, Jain N, Changala B, Patel SD *et al* (2012). Convergent functional genomics of schizophrenia: from comprehensive understanding to genetic risk prediction. *Mol Psychiatry* **17**: 887–905.

Luoni A, Massart R, Nieratschker V, Nemoda Z, Blasi G, Gilles M *et al* (2016). Ankyrin-3 as a molecular marker of early-life stress and vulnerability to psychiatric disorders. *Transl Psychiatry* **6**: e943.

Malki K, Du Rietz E, Crusio WE, Pain O, Paya-Cano J, Karadaghi RL *et al* (2016). Transcriptome analysis of genes and gene networks involved in aggressive behavior in mouse and zebrafish. *Am J Med Genet B Neuropsychiatr Genet* **171**: 827–838.

Niculescu AB 3rd, Segal DS, Kuczenski R, Barrett T, Hauger RL, Kelsoe JR (2000). Identifying a series of

candidate genes for mania and psychosis: a convergent functional genomics approach. *Physiol Genomics* **4**: 83–91.

Patel SD, Le-Niculescu H, Koller DL, Green SD, Lahiri DK, McMahon FJ *et al* (2010). Coming to grips with complex disorders: genetic risk prediction in bipolar disorder using panels of genes identified through convergent functional genomics. *Am J Med Genet B Neuropsychiatr Genet* **153B**: 850–877.



This work is licensed under a Creative Commons Attribution 4.0 International License. The images or other third party material in this article are included in the article's Creative Commons license, unless indicated otherwise in the credit line; if the material is not included under the Creative Commons license, users will need to obtain permission from the license holder to reproduce the material. To view a copy of this license, visit <http://creativecommons.org/licenses/by/4.0/>

© The Author(s) 2018

Neuropsychopharmacology Reviews (2018) **43**, 227–228.
doi:10.1038/npp.2017.221

A Translational Model to Assess Sign-Tracking and Goal-Tracking Behavior in Children

Cues or stimuli in the environment can guide behavior in adaptive ways, bringing one in close proximity to valuable resources (for example, food). For some individuals, however, environmental stimuli may acquire inordinate control over behavior and elicit maladaptive tendencies or intrusive thoughts. Thus, the way an individual responds to cues in the environment may be a key determinant of psychopathology. For example, in addiction, relapse is most often triggered by exposure to stimuli (for example, paraphernalia or places) previously associated with the drug-taking experience, and people suffering from post-traumatic stress disorder (PTSD) experience extreme anxiety or flashbacks upon exposure to stimuli reminiscent

of a traumatic event. Furthermore, in patients with schizophrenia, psychosis is believed to result from aberrant attribution of motivational salience to environmental stimuli (Kapur, 2003). Such stimuli are able to elicit complex emotional and motivational states via Pavlovian learning, and in recent years we have come to rely on an animal model to better understand these processes (for review see Robinson *et al*, 2014).

When exposed to a Pavlovian conditioning paradigm wherein the presentation of a lever (conditioned stimulus, CS) is followed by delivery of a food reward (unconditioned stimulus, US), some rats, termed 'goal-trackers' (GT), attribute *predictive value* to the lever-cue and go to the location of food delivery upon cue presentation. Others, termed 'sign-trackers' (ST), also attribute *incentive salience* to the lever-cue, as evidenced by their approach towards the cue and the ability of the cue alone to act as a reinforcer (for review see Robinson *et al*, 2014). That is, for ST the reward cue attains excessive incentive motivational value and gains inordinate control, leading to maladaptive behaviors. Indeed, relative to GT, ST have also been shown to be more impulsive, more likely to exhibit cue-induced relapse to drug-seeking behavior after relatively little drug exposure, and more susceptible to abnormal fear responses upon exposure to aversive stimuli (for review see Robinson *et al*, 2014). Thus, examining the translational relevance of the sign-tracker/goal-tracker model may prove critical to our understanding of a number of cue-motivated psychopathologies, including impulse control disorders, addiction and post-traumatic stress disorder.

To-date, little research has directly examined sign- and goal-tracking behavior in humans (Garofalo and di Pellegrino, 2015), and, to our knowledge, none with children. Due to the delayed development of the prefrontal cortex (Casey *et al*, 2000), children may be more likely to exhibit sign-tracking behavior. Indeed, the lack of cortical control and associated attentional deficits and impulsive behavior